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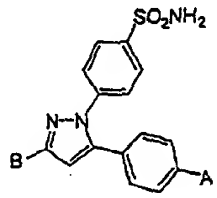
(54) Title: SYNTHESIS OF 4–[(5–SUBSTITUTED OR UNSUBSTITUTED PHENYL) –3–SUBSTITUTED –1H–PYRAZOL –1–YL] BENZENESULFONAMIDES



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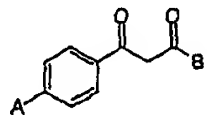

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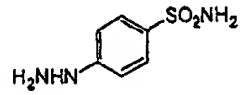

(III)

(57) Abstract

This invention encompasses a novel process for synthesizing the compound represented by formula (I) or a salt, hydrate or solvate thereof, wherein A represents H, halo, or methyl, and B represents CH_3, CH_2F, CHF_2 OR CF_3, comprising reacting a compound of formula (II) with a compound of formula (III) or a salt or hydrate thereof, in an amide solvent at a controlled temperature to produce a compound of formula (I). These compounds are useful as non–steroidal anti–inflammatory agents.

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TITLE OF THE INVENTION

SYNTHESIS OF 4-[(5-SUBSTITUTED OR UNSUBSTITUTED PHENYL)-3-SUBSTITUTED-1H-PYRAZOL-1-YL]BENZENESULFONAMIDES

BACKGROUND OF THE INVENTION

This application is directed to an improved process for making 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide. A general process is disclosed in U.S. Patent No. 5,466,823 and Penning et al., J. Med. Chem., Vol. 40, pp. 1347-1365, 1997. The process described herein yields a product with a higher ratio of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide with respect to its regioisomer, a higher yield and greater degree of purity than the previously disclosed process. The compound is generally useful as a non-steroidal antiinflammatory agent.

Non-steroidal, antiinflammatory drugs (NSAIDs) exert most of their antiinflammatory, analgesic and antipyretic through an inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Initially, only one form of cyclooxygenase was known, this corresponding to cyclooxygenase-1 (COX-1) or the constitutive enzyme. More recently, a second inducible form of cyclooxygenase, COX-2, has been characterized. This enzyme is distinct from the COX-1 enzyme. COX-2 is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. The constitutive enzyme, COX-1, is responsible in large part for endogenous basal release of prostaglandins and hence is important in physiological functions, such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, COX-2, is mainly responsible for the pathological eff cts of prostaglandins where rapid induction of

the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines.

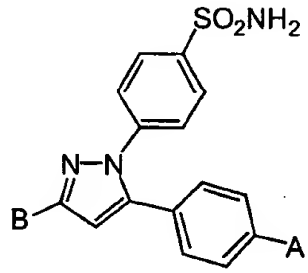
A brief description of the potential utility of cyclooxygenase-2 inhibitors is given in an article by John Vane, Nature, Vol. 367, pp. 215-216, 1994, and in an article in Drug News and Perspectives, Vol. 7, pp. 501-512, 1994.

Thus, one object of the present invention is to provide a process that yields a product with a higher ratio of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide with respect to its regioisomer.

Another object of the present invention is to provide a process with a higher yield and greater degree of purity. These and other objects will be apparent to those of ordinary skill from the teachings contained herein.

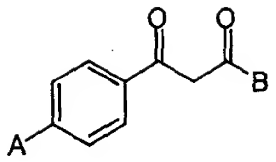
SUMMARY OF THE INVENTION

This invention encompasses a novel process for synthesizing the compound represented by formula I:



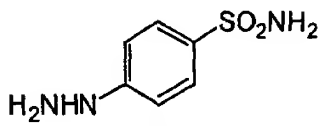
I

or a salt, hydrate or solvate thereof, wherein A represents H, halo, or methyl, and B represents CH_3, CH_2F, CHF_2 or CF_3 , comprising reacting a compound of formula II:



II

with a compound of formula III:

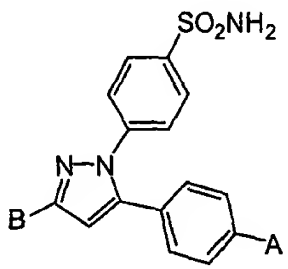


III

or a salt or hydrate thereof, in an amide solvent at a controlled temperature to produce a compound of formula I.

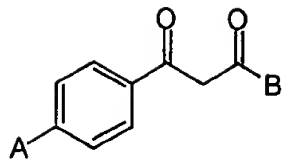
DETAILED DESCRIPTION OF THE INVENTION

This invention encompasses a novel process for synthesizing a compound represented by formula I:



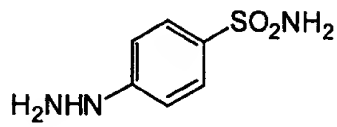
I

or a salt, hydrate or solvate thereof, wherein A represents H, halo, or methyl, and B represents CH_3 , CH_2F, CHF_2 or CF_3 , **comprising reacting a compound of formula II:**



II

with a compound of formula III:



III

or a salt or hydrate thereof, in an amide solvent at a controlled temperature to produce a compound of formula I.

In a preferred embodiment, the amide solvent is selected from N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidinone, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone and 1,1,3,3-tetramethylurea.

In another embodiment, the controlled temperature does not exceed about 30° C.

In yet another embodiment, the amount of the regioisomer of formula I in the product is about 0.5% or less, and the product yield is at least about 80%.

A preferred embodiment is that wherein the compound of formula I is about 99% pure.

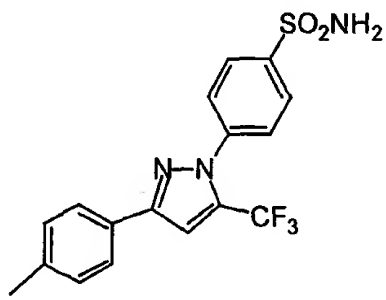
Of particular interest are compounds of formula I produced as a solvate of the amide solvent. More particluarly, this invention encompasses recrystallizing the amide solvate of the compound of formula I from isopropanol and water to produce an unsolvated compound of formulaI.

For the purposes of this specification, the term "amid solvent" refers to N,N-dimethylformamide, N,N-

dimethylacetamide as well as the other solvents that are described above. Ethereal solvents are disclosed in some of the examples and tables for comparison purposes.

The term "controlled temperature" means a threshold reaction temperature under which the reaction temperature is mainatined. An example of a controlled temperature is about 30° C.

The term regioisomer refers to the following structure:



Regioisomer

The points of attachment of the CF_3 group and the 4-B-phenyl group on the pyrazole ring are reversed.

The invention is further illustrated by the following non-limiting examples:

PREPARATIVE EXAMPLE 1

4,4,4-Trifluoro-1-(4-methylphenyl)-butane-1,3-dione

Under nitrogen, to a 100 L three-necked round bottom flask equipped with a mechanical stirrer, a nitrogen inlet and a thermocouple charge lithium hexamethyldisilazide (LHMDS) and tetrahydrofuran (THF) (25.0 l, KF = 80) at -60° C. Add 4-methylacetophenone over 30 min. Age the mixture at -60° C for 30 min. Add 2,2,2-trifluroroethyl trifluoroacetate over 30 min, maintaining the temperature at lower than -50° C during the additions. Age the mixtur for 20 hrs at ambient temperature.

Allow the mixture to come to 0°C. Add 3N HCl slowly so that the temperature is maintained at less than 20° C. Age the mixture for 30 min. Separate in the separatory cylinder (100 L) give the THF layer. Concentrate and switch solvents to acetonitrile (ACN). Add ACN to a volume of 12 L. Cool the solution to -10° C. Add H_2O (8.0 L).

Slowly add additional H_2O (45.0 L). Age the mixture at ambient temperature for 3 hrs. Isolate the solid by filtration via an insulated sintered funnel. Rinse the wet cake with H_2O (20.0 L). Dry under reduced pressure to afford 3.68 kg (approx) of the product at 86% yield.

EXAMPLE 1

4-[5-(4-METHYLPHENYL)-3-(TRIFLUOROMETHYL)-1H-PYRAZOL-1-YL]BENZENESULFONAMIDE

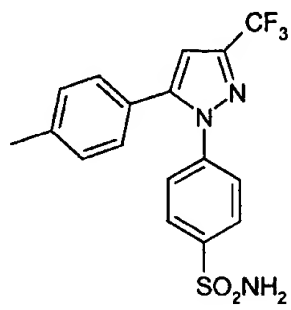
Step 1 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide·DMAC

Under nitrogen, to a 100 L three-necked round bottom flask equipped with a mechanical stirrer, a nitrogen inlet and a thermocouple, charge 4,4,4-trifluoro-1-(4-methylphenyl)-butane-1,3-dione (2.0 kg), 4-sulphonamidophenylhydrazine hydrochloride (1.943 kg) and N,N-dimethylacetamide (DMAC) (40.0 L) at ambient temperature. Slowly add HCl (12 N) (0.36 L) over 30 min. Age the mixture at ambient temperature for 24 hrs. Slowly add H_2O (40.0 L) over 20 min. Age the mixture for 20 hrs at ambient temperature. Keep the reaction temperature under 30° C. The addition of H_2O is slightly exothermic and the temperature should be controlled under 30° C during the addition. Isolate the solid by filtration via an insulated sintered funnel. Rinse the wet cake with cold DMAC and water (10-12 L).

Step 2 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

Under nitrogen, to a 100 L three-necked round bottom flask equipped with a mechanical stirrer, a nitrogen inlet and a thermocouple charge 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide·DMAC (3.3kg) and isopropanol (IPA) (24 L). Heat the mixture to 50° C. Transfer the solution to another 100 L vessel via a pump going through a 1 micron filter to remove insoluble particles. Rinse with more IPA (2.4 L). Slowly add H_2O (39.6 L) over 130 min. Age for 2 hrs at ambient temperature. Isolate the solid by filtration. Wash the cake two times with IPA/water (1:1.5) and two times with water. Dry at 45° C for 96 hrs. The yield is approximately 2.7 kg (89.6 %).

COMPARATIVE EXAMPLE 2



In a 250ml round bottom flask combine 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione (3.68g, 16mmol), 4-sulfonamidophenylhydrazine hydrochloride (3.58g, 16 mmol), MTBE (9ml), methanol (2.5ml), ethanol (100ml) and 4N HCl (4.0 ml, 16mmol). Heat the mixture to reflux for 3 hours. A sample assayed by HPLC shows 2.6A% of regioisomer. The mixture is cooled, and concentrated under vacuum to 60ml. Water (30ml) is added dropwise, during which the product crystallizes. The mixture is aged for 1 hour at room temperature, filtered, washed with ethanol/water (20ml 60% ethanol, v/v), and water (20ml). The solid is dried under vacuum at 45°C.

Yield, 4.7g (76.4%).
HPLC assay 99.1 wt%, with 0.57A% regioisomer.
MP. 160.5-162.3°C

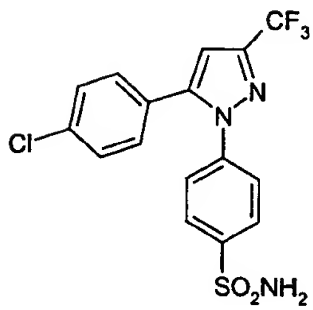
EXAMPLE 3

In a 100ml round bottomed flask combine 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione (2g, 8.68 mmol), 4-sulfonamidophenylhydrazine hydrochloride (1.95g, 8.68 mmol), DMPU (40ml), 6N HCl (1.4 ml, 8.68 mmol). Stir the mixture for ~16 hours at ambient temperature. A sample assayed by HPLC shows 0.16A% of regioisomer. Water (40ml) is added dropwise, during which the product crystallizes. The mixture is aged for ~4 hours at room temperature, filtered, washed with DMPU/water (10ml, 1:1 v/v), and water (20ml). The solid is dried under vacuum at 45°C.
Yield, 3.7g 1:1 DMPU solvate, 2.76 assay g (83%).
HPLC assay 74.8 wt%, with 0.04A% regioisomer.
MP. 145-146°C

EXAMPLE 4

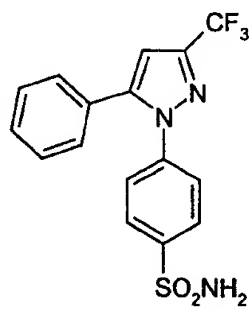
In a 100ml round bottomed flask combine 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione (2g, 8.68 mmol), 4-sulfonamidophenylhydrazine hydrochloride (1.95g, 8.68 mmol), NMP (40ml), 6N HCl (1.4 ml, 8.68 mmol). Stir the mixture for ~16 hours at ambient temperature. A sample assayed by HPLC shows 0.27A% of regioisomer. Water (40ml) is added dropwise, during which the product crystallizes. The mixture is aged for ~4 hours at room temperature, filtered, washed with DMPU/water (10ml, 1:1 v/v), and water (20ml). The solid is dried under vacuum at 45°C.
Yield, 3.5g 1:1 NMP solvate, 2.8 assay g (85%).
HPLC assay 80 wt%, with 0.03A% regioisomer.
MP. 137-139°C

EXAMPLE 5



In a 100ml round bottomed flask combine 1-(4-chlorophenyl)-4,4,4-trifluorobutane-1,3-dione (1.0g, 3.98 mmol), 4-sulfonamidophenylhydrazine hydrochloride (0.89, 3.98 mmol), DMAc (20ml), 6N HCl (0.64 ml, 3.98 mmol). Stir the mixture for ~16 hours at ambient temperature. A sample assayed by HPLC shows 0.49A% of regioisomer. Water (20ml) is added dropwise, during which the product crystallizes. The mixture is aged for ~4 hours at room temperature, filtered, washed with DMAc/water (5ml, 1:1 v/v), and water (20ml). The solid is dried under vacuum at 45°C. Yield, 1.56g 1:1 DMAc solvate, (80%).
HPLC assay 0.07A% regioisomer.
MP. 141.5-143.5°C

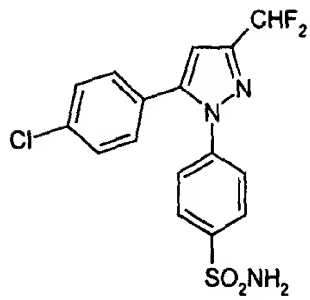
EXAMPLE 6



In a 100ml round bottomed flask combine 1-(phenyl)-4,4,4-trifluorobutane-1,3-dione (2.0g, 12.3 mmol), 4-sulfonamidophenylhydrazine hydrochloride (2.7g, 12.3 mmol), DMAc (40ml), 6N HCl (2.0 ml, 12.3 mmol). Stir the mixture for ~16 hours at ambient temperature. Water (40ml) is added dropwise, during which the product crystallizes. The mixture is aged for ~4 hours at room temperature, filtered, washed with DMAc/water (10ml1:1 v/v), and water 20ml. The solid is dried under vacuum at 45°C.

Yield, 3.8g 1:1 DMAc solvate, (85.3%).
HPLC assay 0.07A% regioisomer.
MP. 113-115°C

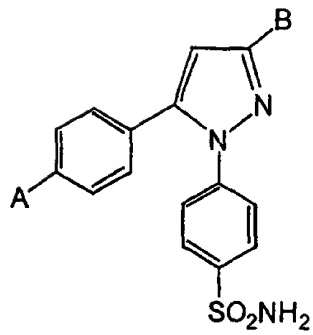
EXAMPLE 7



In a 100ml round bottomed flask combine 1-(4-chlorophenyl)-4,4-difluorobutane-1,3-dione (1.0g, 3.98 mmol), 4-sulfonamidophenylhydrazine hydrochloride (0.89, 3.98 mmol), DMAc (20ml), 6N HCl (0.64 ml, 3.98 mmol). Stir the mixture for ~16 hours at ambient temperature. A sample assayed by HPLC shows 1.16A% of regioisomer. Water (20ml) is added dropwise, during which the product crystallizes. The mixture is aged for ~4 hours at room temperature, filtered, washed with DMAc/water (5ml, 1:1 v/v), and water (20ml). The solid is dried under vacuum at 45°C.
Yield, 1.9g 1:1 DMAc solvate, 94(80%).
HPLC assay 0.03A% regioisomer.
MP. 133-135°C

Compounds can be prepared in accordance with the procedures described in the examples, using the solvents disclosed in Table 1, and the yields and level of purity relative to the regioisomers are as described below.

TABLE 1

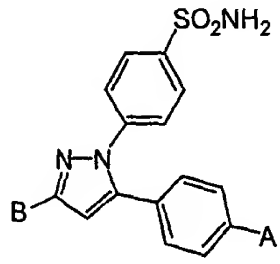


A	B	Solvent	Solvate	A% regio*	MP °C	Yield %
CH_3	CF_3	DMAc	1:1	0.02	148-149.5	83
CH_3	CF_3	DMF	1:1	-	129-131	84
CH_3	CF_3	NMP	1:1	0.03	137-139	85
CH_3	CF_3	DMPU	1:1	0.04	145-146	83
CH_3	CF_3	TMU	1:1	0.06	105-107	79
CH_3	CF_3	Ethanol	-	0.57	160.5-162.3	76.4
H	CF_3	DMAc	1:1	0.07	113-115	85.3
H	CF_3	DMF	-	0.18	164-165.5	80
Cl	CF_3	DMAc	1:1	0.07	141.5-143.5	80
Cl	CF_3	DMF	1:1	0.18	92.5-93.5	79
Cl	CHF_2	DMAc	1:1	0.03	133-135	94
Cl	CHF_2	DMF	-	0.03	187-189	80

MTBE = methyl t-butyl ether
DMAc = N,N-Dimethyl-acetamide
DMF = N,N-Dimethyl-formamide
NMP = 1-Methyl-2-pyrrolidinone
DMPU = 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
TMU = 1,1,3,3-Tetram thylurea
* = As measured by HPLC

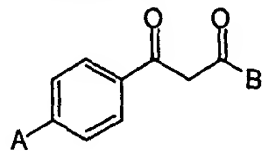
WHAT IS CLAIMED:

1. A process of synthesizing a compound represented by formula I:



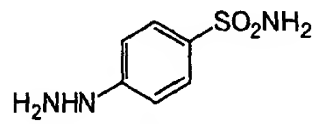
I

or a salt, hydrate or solvate thereof, wherein A represents H, halo, or methyl, and B represents CH_0 , CH_2F, CHF_2 or CF_3 , comprising reacting a compound of formula II:



II

with a compound of formula III:



III

or a salt or hydrate thereof, in an amide solvent at a controlled temperature to produce a compound of formula I.

2. A process according to Claim 1 wherein the amide solvent is selected from the group consisting of:

N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidinone, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone and 1,1,3,3-tetramethylurea.

3. A process according to Claim 1 or 2 wherein the controlled temperature does not exceed about 30° C.

4. A process according to Claim 1, 2 or 3 wherein the amount of the regioisomer of formula I in the product is about 0.5% or less, and the product yield is at least about 80%.

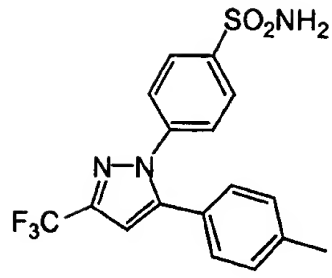
5. A process according to Claim 1, 2, 3 or 4 wherein the compound of formula I is about 99% pure.

6. A process in accordance with Claim 1, 2, 3 or 4 wherein the compound of formula I is produced as a solvate of the amide solvent.

7. A process according to Claim 6 further comprising recrystallizing the amide solvate of the compound of formula I from isopropanol and water to produce an unsolvated compound of formula I.

8. A process in accordance with claim 1, 2, 3, 4, 5, 6 or 7 wherein A represents CH_3 and B represents CF_3.

9. A compound of the following formula:



as a solvate of DMPU, NMP, DMAc, TMU or DMF.

10. A compound in accordance with claim 9 as a 1:1 solvate.

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/CA 00/00034

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D231/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 37476 A (SEARLE & CO ;ZHI BENXIN (US); NEWAZ MURAD (US); TALLEY JOHN J (US)) 28 November 1996 (1996-11-28) page 14, line 19 - line 34; claims 5-13	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 April 2000	04/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schmid, J-C

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	PENNING ET AL: "Synthesis and Biological Evaluation of the 1,5-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of 4-'5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl!benzenesul fonamide (SC-58635, Celecoxib" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 40, 1997, pages 1347-1365, XP002114833 ISSN: 0022-2623 cited in the application page 1348, left-hand column Scheme 1 page 1350,Scheme 6, step c; page 1355, right-hand column, step 2 ---	1-10
A	US 5 466 823 A (GRANETO MATTHEW J ET AL) 14 November 1995 (1995-11-14) cited in the application column 20, line 41-44; example 1 ---	1-10
A	US 5 475 018 A (LEE LEN F ET AL) 12 December 1995 (1995-12-12) column 5, line 13-21 column 8, line 40-42 Scheme I and II -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

Im .ational Application No
PCT/CA 00/00034

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